IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Ashley Birkett	) PATENT
Serial No.:	09/930,915	) Attorney Docket) LOR-102.2
Filed:	August 15, 2001	) (9720/81175)
For:	IMMUNOGENIC HBc CHIMER PARTICLES HAVING ENHANCED STABILITY	) Group Art No. 1648
Examiner:	Bo Peng	)

APPELLANT'S REPLY BRIEF ON APPEAL

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a Reply Brief filed in response to the Examiner's Answer mailed June 22, 2010. Applicable fees accompany the filing of this brief.

Should there be any deficiency in fees in connection with this Appeal, the Commissioner is respectfully requested to and is hereby authorized to charge any such deficiency in fees to Deposit Account No. 23-0920.

STATUS OF CLAIMS

Claims 1-9, 12-33, 35-38, and 42-78 are pending and have been at least twice and finally rejected. The rejections of claims 1-9, 12-33, 35-38, and 42-78 are being appealed. A copy of the pending claims appears in the Claims Appendix.

In the Examiner's Answer mailed June 22, 2010, the Fifth ground of rejection concerning claims 12-14, 17, 27-29, 36, 37, 59-62 and 76 under 35 USC 102(a) was withdrawn in view of Appellant's argument.

Furthermore, the Sixth ground of rejection concerning claims 1-9, 12-33, 35-38 and 42-78 on the ground of nonstatutory obviousness-type double patenting over claims 98-109 of application serial number 10/805,913 and claims 79-115 of 10/806,006 was found to be moot because those applications were abandoned.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1) Whether Claims 1-9, 12-33, 35-38, and 42-78 are unpatentable under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

2) Whether Claims 1-9, 12-33, 35-38, and 42-78 are unpatentable under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

3) Whether Claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58 63-75, 77 and 78 are unpatentable under 35 U.S.C. §103 as being obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33:63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94:9556-9561).

4) Whether Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 are unpatentable under 35 U.S.C. §103 as being obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33:63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94:9556-9561) as applied to claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58 63-75, 77 and 78, further in view of Thorton et al (U.S. Patent No. 5,143,726).

5) withdrawn by Examiner

6) Whether Claims 1-9, 12-33, 35-38 and 42-78 are unpatentable under obviousness-type double patenting, as being obvious over (1) claims 1-46 of co-pending application

10/732,862; (2) claims 1-53 of 10/787,734; (3) claims 47-85 of 11/508,655; (4) claims 1-22, 25, 26 of 11/507,083.

7) Whether Claims 1-9, 12-33, 35-38, and 42-78 are unpatentable under obviousness-type double patenting, as being obvious over (1) claims 1-19 of U.S. Patent No. 6,213,864 in view of Zlotnick et al. (PNAS, 1997, 94(18): 9556-9561).

ARGUMENT

1) Claims 1-9, 12-33, 35-38, and 42-78

Comply with the Enablement Requirement

In contrast to allegations asserted in the Examiner's Answer of June 22, 2010, claims 1-9, 12-33, 35-38, and 42-78 do satisfy the enablement requirement. Claims 1-9, 12-33, 35-38, and 42-78 were rejected under 35 U.S.C. §112, first paragraph, because the specification, although said to be enabling for a HBc chimer of SEQ IQ NOs:246-251, allegedly does not reasonably provide enablement for a HBc chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID NOs: 246-251, according to the Examiner's Answer, pages 4-5, section 1.

The Answer and previous Actions have concentrated on particle formation, and that is the wrong issue as is discussed below. This assertion of a lack of enablement is mistaken for at least two reasons.

It is first submitted that there is ample evidence in the specification for chimer molecules having no more than about 5% substitution in the HBc sequence that form particles. Figures 7A and 7B of the specification show the HBc amino acid sequences of three human HBc subtypes and two mammalian species, woodchuck and ground squirrel. It can be seen that the amino

acid sequences are similar though not identical, each having numerous amino acid substitutions (about 200 total) as compared to the most preferred subtype HBc *ayw* SEQ ID NO:247. Yet, these sequences all form particles. (See, pages 22 and 47 of the specification.) Neither the Actions nor the Answer has provided any basis to believe that a skilled worker could not use any of those different sequences and not arrive at a particle.

In a similar light, one of the articles mentioned in the specification on page 117, Schodel et al., discussed a loop replacement approach to modification of the HBc sequence, where residues 76-80 of the HBc sequence (the loop region) were substituted by various other amino acids. There the *Plasmodium falciparum* CS sequence of $(NANP)_4$ and the *Plasmodium berghei* CS sequence of $(DP_4NPN)_2$ were substituted for those amino acids (see Figure 1 of Schodel). These HBc sequences with loop amino acid substitutions also formed particles.

Similarly, Example 4 on page 117 of the present specification teaches the CS-2 molecule, which has a deletion of residues 76-82 and a substitution of other amino acids (NANP) that forms particles.

Furthermore, the specification exemplifies amino acid sequence "inserts" into the HBc amino acid sequence that form particles. These molecules having inserted amino acids in fact

have amino acid substitutions at the insert point and after. Table 15 illustrates this concept, as partially reproduced below:

wt HBc	TWVGVNLEDPASRDLVVSYN
HBc150K75	TWVGV**KNLEDPASRDLVVSYN**
HBc150K76	TWVGVN**KLEDPASRDLVVSYN**
HBc150K77	TWVGVNL**KEDPASRDLVVSYN**

So for the HBc150K75 molecule, for instance, the amino acids 75-149 have been substituted from the original HBc sequence. In the specification, various other amino acids were inserted between E77 and D78 (V1 series) and also between amino acids D78 and P79 (V2 series). In addition, there was the V12 series, where B cell epitopes were inserted between amino acids D78 and P79 as well as a T cell epitope downstream of V149. Moreover, there was the lysine loop series (K series) where one lysine residue per molecule was substituted for each residue of the internal loop of HBc. (see pages 140 and 146 and Table 15) These amino acid sequences (V1 series, V2 series, V12 series and K series) had amino acid substitutions in the HBc sequence and formed particles.

Also, the specification recites that substitutions, other than in the immunodominant loop or at the termini, are preferably in the non-helical portions, between residues 1-15

and 24-50, approximately, to help assure particle formation, citing Koschel et al. (see page 48, first paragraph). This provides additional guidance besides the recited LASERGENE software in predicting what substitutions will be tolerated for folding.

Likewise, another article discussed in the specification, Pumpens et al., stated that the sequence of the HBc protein was determined for more than 30 cloned HBV genomes, showing conservation among themselves and core proteins of other mammalian and avian viruses. Pumpens stated that regions around positions 20-25, 30-35, 40-50, 70-80, 90-95, 110, and 125-135 are good candidates for modifications of the HBc sequence. Also Pumpens stated that substitution of the 3 N-terminal amino acids with 8 N-terminal amino acids from another species was done and the protein molecule formed particles. (See, page 5, lines 1-15.)

The specification also cited Kratz et al., who showed that amino acids 79 and 80 could be replaced and the molecule still formed particles. (See, page 6, lines 1-8.)

The specification also mentioned Neirynck et al. on page 33, who showed that residues 1-4 of the native sequence could be substituted and the resulting mutants formed particles.

Another article discussed in the specification was that of Zlotnick et al., who showed that molecules having amino acid substitutions at positions 48, 61, 107 and 150 formed particles. (see page 4, first paragraph).

As further evidence of particles having amino acid substitutions, the specification describes the work of Metzger et al., who showed that substitutions of the 4 prolines in the sequence found in the region of sequence 129-144 formed particles, except for the proline 138 position. Metzger stated that this lack of substitution at this position was predictable and not unexpected because proline 138 plays a crucial role in the assembly of particles. (See, page 589, column 2, of Metzger.) The skilled worker would therefore know to include the proline at position 138 to help assure particle formation.

Thus, if he/she did not already know how to make and use HBc chimer particles, a skilled worker would have been able to make and use such particles from the inventor's teachings in the specification and the teachings of the articles cited throughout the specification, which teachings are directed to workers of ordinary skill in the art. Such particles would, however, not have been within the claimed subject matter, but would rather be the standards against which particles of a

claimed chimer protein molecule would be tested for enhanced stability.

Thus, a chimeric molecule of the claims exhibits the benefit of enhanced stability that is provided by the inclusion of at least one cysteine residue within about 30 residues from the C-terminus of the sequence of the chimer molecule. The specification provides ample evidence of chimeric HBc molecules having one or more C-terminal cysteines that form particles that are more stable upon storage than the otherwise identical particles without the C-terminal cysteine. (See Examples 6 and 7 and Figures 3, 4, and 8. Also see Table 17 on page 165 showing particles having amino acid substitutions and forming particles, namely V2.1A1(290 to 232)*; V12.Pf1(C17A)+C150; V12.Pf1*; HBc150(K77)+C*; HBc150(K79)+C*; and V2.Pf1+CF/HBc74-87+C* that are more stable than identical particles without the terminal cysteine.)

Therefore, one of skill in the art would have no problem understanding, making and using a claimed chimer protein molecule having a native amino acid residue sequence and a C-terminal cysteine, especially after reading that molecules having an amino acid insert and a C-terminal cysteine have successfully formed particles that are more stable on storage than those without the C-terminal cysteine. [See molecules

V2.Pf1+C on page 126; V16.1A1(290 to 302)* on page 165; V12.Pf1(C17A)C150 on pages 162-163 and 165; HBc150(K77)+C on page 165; HBc150(K79)+C on page 165; and V2.Pf1+CF/HBc74-87+C on page 165 among others].

The Answer stated that the specification has not shown any HBc sequence having up to 5% substituted amino acid residues in the HBc sequence with enhanced stability, but rather has only shown native chimers having enhanced stability. (See the last line of page 19.) It is submitted that a chimer molecule whose HBc portion is that of SEQ ID NO:247 contains "no more than about 5 percent substituted amino acid residues in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149" as is recited in the claims. There are, in fact, many such sequences shown in the specification whose particles exhibited enhanced stability as compared to particles of a sequence without a claimed C-terminal cysteine.

The Answer also stated that the constructs V2.Pf1+C150 and V12.Pf1+C150 comprise an HBc sequence 100% identical to human HBc of SEQ ID NO:247 and therefore HBc chimers containing about 5% unspecified mutations are not enabled. (See, Answer, page 19, section 30.) That the HBc sequence portions are identical does not speak to a lack of enablement. The chimeric protein constructs of VPf1+C150 and V12.Pf1+C150 have relatively

large inserts into their immunogenic loops (bold type below), and their particles exhibited enhanced stability as compared to the identical molecule without a C-terminal cysteine. (See, Figure 3 and Tables 17-19)

amino acid	1	77	149
wt HBc	MDIDPYKEFG…E	DPASRDLVVSYVN…V	
V2.Pf1+C150	MDIDPYKEFG…E	**GINANPNANPNANPNANPEL**	DPASRDLVVSYVN…VC
V12.Pf1+C150	MDIDPYKEFG…E	**GINANPNANPNANPNANPEL**	DPASRDLVVSYVN…VC…

The primary bases of the various Actions and the Answer for the assertion that the full breadth of the subject matter claimed is not enabled are the misapprehension of what the skilled worker would take away from reading the specification, including the Metzger paper and its admonition about the effects of an absence of a proline at position 138, and that no specific examples of chimer proteins with conservative substitutions in the HBc sequence portion have been shown.

The Court in *In re Strahilevitz,* 212 USPQ 561; 668 F.2d 1229 (Fed. Cir. 1982) held that where there were there were sufficient literature citations to establish both the level of ordinary skill in the art and the fact that the techniques

necessary to practice the invention were known in the art, enablement could be found. It is submitted that far more was present here than in *Strahilevitz*. Not only is the specification rife with literature citations that here also set the level of skill in the art as well as show that a skilled worker could make and use the claimed subject matter, but the specification contains several actual examples of subject matter that falls within the claims. *Strahilevitz* had no such examples.

The absence of an understanding of what the Metzger teaching disclosed in the specification would teach a skilled worker having been dealt with, the only basis remaining for the rejection is an amorphous and unsupported assertion of a lack of enablement. The Court in *In re Marzocchi & Horton*, 439 F.2d 220, 223; 169 USPQ 367, 369-370 (CCPA 1971) ruled upon the propriety of a similar rejection in a chemical application. The Court held that the

> only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion [of efficacy]. [169 USPQ at 369; emphasis in the original.]

The Court went on to hold:

> it is encumbent upon the Patent Office, whenever a rejection on this basis [doubt as to enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate statement. (Emphasis in the original.)

The *Marzocchi* requirement of an explanation of "why" truth or accuracy of the disclosure is doubted has not been complied with in that neither the Actions nor the Answer have provided "acceptable evidence or reasoning which is inconsistent with the contested statement". Metzger teaches what should be done to get particles. Pumpens tells where one can make appropriate substitutions, as does the specification. The specification also teaches how to make and use numerous sequences that form particles and shows that adding the C-terminal cysteine aids stability of those particles once formed.

Thus, the claims are enabled. It is therefore respectfully requested that this rejection be withdrawn.

2) Claims 1-9, 12-33, 35-38, and 42-78 Comply with the Written Description Requirement

In contrast to allegations asserted in the Examiner's Answer, claims 1-9, 12-33, 35-38, and 42-78 do satisfy the written description requirement. The Answer alleged that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention under 35 USC 112, first paragraph.

It is noted that the Answer acknowledged that arguments and evidence presented in the Final Action were directly copied and pasted from another Action in another case entirely. Specifically this material was copied from application 10/732,862, filed 12-10-03.

The Answer then went on to state that application 10/732,862 is directed to the same subject matter as the instant application; i.e., HBc chimers with enhanced stability. Although broadly true, this is a mischaracterization of the language of the claims of both applications.

The Answer then stated that Example 14 of that application showed that only 7 out of 24 HBc chimers in that set were able to yield particles. This statement is irrelevant to the issue of the written description requirement as applied to

the present claims. Neither set of claims is directed to whether or not HBc sequences yield particles. The claims here are directed to particles that are more stable than identical particles without C-terminal cysteines. There is no information in that Table 13 regarding the stability of any molecule. This argument is altogether off-base.

Moreover, the Answer's next statement that 14 of the 24 tested HBc chimers lost their ability to form particles in Table 13 makes no sense. First the phrase "lost their ability to form particles" means that they first had an ability then they lost it. The Table does not speak to that. Second, there are no data that show that 14 of the chimers did or did not exhibit something unlike the other chimers. The entire argument in this section of the Answer makes no sense.

As to the allegations in section 37, that "substitution of a single amino acid change can result in an unpredictable effect on the ability to assemble of HBc particles", citing Metzger and Example 14 of 10/732,862, this is irrelevant to a decision of whether the current claims satisfy the written description requirement. Metzger did not address chimers having C-terminal cysteines having enhanced stability as compared to those not having that limitation nor does 10/732,862. Furthermore, a skilled worker reading the

specification would see what Metzger found and keep the proline at position 138 if particles were to be made.

As extensively illustrated in the previous section of this Reply Brief, ample data have been provided in the specification to show that the Applicant was indeed in possession of the claimed invention. There was actual reduction to practice of molecules having less than 5% amino acid substitutions, a heterologous epitope/linker, and a C-terminal cysteine that were more stable than identical molecules without the C-terminal cysteine. Specifically, see molecules V2.Pf1+C on page 126; V16.1A1(290 to 302)* on page 165; V12.Pf1(C17A)C150 on pages 162-163 and 165; HBc150(K77)+C on page 165; HBc150(K79)+C on page 165; and V2.Pf1+CF/HBc74-87+C on page 165 among others. Therefore, it is respectfully requested that this rejection be withdrawn.

As an additional point, according to the MPEP, section 2163, Section I, it is now well accepted that a satisfactory description may be in the claims or any other portion of the originally filed specification, citing *In re Koller*, 613 F.2d 819, 204 USPQ 702 (CCPA 1980) (original claims constitute their own description); accord *In re Gardner*, 475 F.2d 1389, 177 USPQ 396 (CCPA 1973); accord *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) Claim 1 on page 177 of the originally filed

application contains a satisfactory description of these claims. It recites, in essence, a chimer HBc protein molecule that contains… one to ten cysteine residues… and no more than 20 percent conservatively substituted amino acid residues…being more stable than particles formed from an otherwise identical HBc that lacks the C-terminal residues. Therefore, this rejection should be withdrawn.

3) A *Prima Facie* Case of Obviousness of Claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 Has Not Been Established

In contrast to allegations asserted in the Examiner's Answer, claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 are not obvious over the teachings of Pumpens et al. (*Intervirology*, 1995, vol. 33:63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94:9556-9561). The Answer alleges that the combined teachings of Pumpens and Zlotnick teach all the limitations of the claims. We disagree.

Pumpens does not teach or suggest adding 1-10 C-terminal cysteines to stabilize the chimeric molecule and that these particles are more stable than chimers without the C-terminal cysteine residues.

Likewise, Zlotnick does not teach or suggest adding 1-10 cysteine residues at the C-terminus of the particle and that these particles are more stable than chimers without the C-terminal cysteine residues. Zlotnick also does not teach or suggest a conjugated epitope present in the HBc immunodominant loop.

The Answer stated on page 25 that Zlotnick's Cp*150 particles are more stable than Cp*149 particles, citing Figure 1a of Zlotnick as evidence. Figure 1a is a simple schematic of amino acid sequences and alignment of those sequences. There is no information regarding stability of those molecules in that Figure. As there is no basis for the stability argument, the rejection should be withdrawn.

It has repeatedly been pointed out in prior Responses that Zlotnick teaches away from the inclusion of a C-terminal cysteine, because Zlotnick teaches that there is no advantage in having a C-terminal cysteine in his gold-labeled molecule. In the Abstract, Zlotnick states that the HBc chimer having a cysteine at the 150 position that is bonded to a gold cluster is "unimpaired in its ability to form capsids." This teaches one of skill in the art that this molecule, although it has no free C-terminal cysteine, was able to form capsids. This teaches

that the C-terminal cysteine it not important for capsid formation or stabilization.

If the C-terminal cysteine were important for particle formation and stabilization, as the Answer alleges, why was this fact not mentioned in the Abstract, yet the fact that the gold-labeled particle still formed particles was highlighted there.

Next, in the *very first sentence* of the Results and Discussion section, Zlotnick emphasized that purified Cp*149 and Cp*150 assembled into capsids under the same conditions as did other Cp constructs, with or without DTT. (See, page 9558, first par.) Cp*149 has no cysteines, yet it still assembled into stable particles. Cp*150 in DTT, the reduced form, still assembled into stable particles. These facts also teach that the C-terminal cysteine is not important from Zlotnick's point of view.

Moreover, in the second sentence of the Results and Discussion section, Zlotnick emphasizes that the Cp*149 and Cp*150 capsids were *indistinguishable* by negative staining electron microscopy and sedimentation on sucrose gradients. Again this teaches one of skill in the art that there seems to be no advantage in having a C-terminal cysteine.

In addition, Zlotnick suggests that other forces are at work besides cysteine binding in terms of capsid assembly.

He states that binding of a gold cluster, Au11 (monomaleimidyl-undecagold), to Cp*150 induces capsid assembly. He suggests that this binding of Au11 may induce small changes in molecular surfaces near the C-terminus that dock together when dimers polymerize and stimulate the assembly process. (See, page 9560, col. 2, first par.) Zlotnick states that the data show that the gold cannot cross-link subunits nor coordinate C-terminal cysteines, yet the binding of Au11 to Cp*150 induces capsid assembly. Therefore, one of skill in the art would not conclude that C-terminal cysteines are responsible for capsid stabilization, but rather the opposite, that they are not important to that stabilization.

It is heavily emphasized in Zlotnick that the molecules with no freely available C-terminal cysteines still form particles. It has repeatedly been stated that Cp*149 forms particles, Cp*150 in DTT forms particles, and gold-labeled Cp*150 forms particles. It has also been emphasized that these particles form under the same conditions as particles without C-terminal cysteines and that these were indistinguishable from them. This is a substantial amount of evidence that was included to teach one of skill that C-terminal cysteines are not important for capsid formation and stabilization. Therefore, in light of this teaching away from the present claims, there would

be not basis for the skilled worker to add a C-terminal cysteine to her/his HBc chimer construct. It is respectfully requested that this rejection be withdrawn.

The Answer puts a great emphasis on Figure 2b of Zlotnick as a factual basis for finding obviousness. The related arguments are based on a misinterpretation of Figure 2, and previous responses have responded to those misinterpretations. Upon a further reading of Zlotnick, that misunderstanding of the disclosure has become apparent as is discussed below.

Zlotnick's Figure 2 compares the elution profiles of a 150-mer gold-cluster-labeled HBc 150-mer particle, a HBc 150-mer particle in DTT, and a HBc 149-mer particle, after treatment of those particles with urea, as explained in the Materials and Methods section, page 9557 paragraphs 1 and 2. The title of that section is "**Preparation and Biochemical Studies of Gold-Labeled Cp*150.**" As the present claims do not recite a gold-labeled particle, a particle in DTT, or a particle without a C-terminal cysteine, this Figure is not relevant to the present claims.

Zlotnick specifically states in the second full paragraph that Cp*150 was reduced and added to an excess of monomaleimidyl-undecagold, then separated on a Sephacryl column

and eluted in 0.5 ml fractions. The next sentence states that capsids eluted in the void volume at 3-4 ml, free dimers at 5-6 ml, and free Au11 at about 8 ml, citing Figure 2. If one of skill in the art examined Figure 2, a large peak would be seen at about fractions 8-10, which correspond to the gold-labeled capsid, which reportedly elutes at about 4-5 ml. These gold-labeled capsids elute slightly earlier than the Cp*149 capsids and Cp*150 in DTT capsids, which makes sense because both would be a little smaller as neither has attached gold clusters. The next spikes are for the dimers, which elute at about fraction 12, corresponding to about 6 ml.

The Answer emphasizes the sentence: "[t]hese bonds stabilize the quaternary structure of the capsid, as attested by the observation that oxidized Cp*150 capsids-unlike CP*149 capsids or reduced Cp*150 capsids-are resistant to dissociation by 3.5 M urea (Fig. 2b)." (see page 27) As described above, Figure 2b refers to gold-cluster-labeled capsids, which the present claims do not recite. Therefore this sentence and all its alleged implications are not relevant to the present claims.

The Answer next emphasizes the sentences: "[g]enerally, when Cp proteins are stored in low ionic strength, high pH buffer, they do not polymerize. However, when stored in this buffer without DTT, Cp*150 dimers assemble into capsids."

(see page 27) This is also irrelevant to the present claims, which do not specify low ionic strength and high pH. Zlotnick states that under "normal" conditions, purified Cp*149 and Cp*150 assemble into capsids under the same conditions as other Cp constructs, with or without DTT. (See, page 9558, first paragraph.)

Therefore, the present claims are not *prima facie* obvious over Pumpens in view of Zlotnick. The two teachings have no common basis from which a skilled worker could make the combination needed to arrive at the claimed subject matter. It is respectfully requested that this rejection be withdrawn.

4) A *Prima Facie* Case of Obviousness of Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 Has Not Been Established

Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 are not obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33:63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94:9556-9561) as applied to claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58 63-75, 77 and 78, further in view of Thorton et al. (U.S. Patent No. 5,143,726) as alleged in the Action.

The shortcomings of the combination of Pumpens and Zlotnick have been presented above. In short, Pumpens does not teach adding 1-10 C-terminal cysteines to stabilize the

C-truncated chimeric molecule. Further, Zlotnick does not teach a conjugated epitope present in the HBc immunodominant loop in conjunction with 1-10 cysteine residues at the C-terminus of the particle and that these particles are more stable than chimers without the C-terminal cysteine residues.

Thorton, likewise, does not teach the placement of C-terminal cysteines that stabilize a polypeptide molecule relative to a molecule without those cysteines. The Action argued that Thorton teaches the use of chemically modified residues on HBc for the purpose of attaching a conjugated epitope, citing the Abstract, and last paragraph of column 15. (see page 29 of the Answer, line 5-7) The Action argued that the chemically modified residues are functional equivalents of a heterologous linker residue. This alleged equivalency is disagreed with.

One of skill in the art would recognize that a chemically modified amino acid residue is structurally and functionally not the same as a residue in its native state. To suggest that they are interchangeable is not agreed with. Therefore, the rejection based on Pumpens in view of Zlotnick and Thorton should be withdrawn.

It is further noted that the Thornton patent teaches the use of full-length HBc, and has no teaching of the use of

C-terminally truncated HBc molecule. Inasmuch as the present claims do not encompass a full-length HBc molecule, nor can it be agreed that properties of the full-length protein molecule can be *a priori* presumed to be the same for a truncated loop insertion-containing protein of the claims. It is again submitted that the present claims would not be obvious to a forward-looking skilled worker at the time of the invention from the asserted combination of teachings.

5) Withdrawn by Examiner

6) Claims 1-9, 12-33, 35-38 and 42-78 Are Not Obvious under the Doctrine of Obviousness-Type Double Patenting

The Action asserted that claims 1-9, 12-33, 35-38 and 42-78 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (1) claims 1-46 of 10/732,862; (2) claims 1-53 of 10/787,734; (3) claims 98-109 of 10/805,913; (4) claims 79-115 of 10/806,006; (5) claims 47-85 of 11/508,655; (6) claims 1-22, 25, 26 of 11/507,083.

The Examiner's comments about obviousness-type double patenting are noted. In the event that any of the current claims are ultimately allowed and any of the claims of the

above-noted application are allowed, the filing of a terminal disclaimer will be examined in view of the allowed claims of both applications. It is believed to be premature to deal with a terminal disclaimer at the present time.

7) Claims 1-9, 12-33, 35-38 and 42-78 Are Not Obvious under the Doctrine of Obviousness-Type Double Patenting

The Action asserted that claims 1-9, 12-33, 35-38 and 42-78 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (1) claims 1-19 of U.S. Patent No. 6,231,864 to Birkett in view of Zlotnick et al. [PNAS, 1997, 94(18):9556-9561].

The Examiner's comments about obviousness-type double patenting are again noted. In the event that any of the current claims are ultimately allowed, the filing of a terminal disclaimer will be examined in view of the language of the allowed claims and those of the patent. It is believed to be premature to deal with a terminal disclaimer at the present time.

In addition, there is serious doubt as to whether the teachings of Zlotnick and those of the Birkett are properly combinable. Birkett deals only with full-length HBc, having all of its cysteines. Zlotnick has the several deficiencies

discussed above. As such, without a hindsight reconstruction, it is difficult to see how a forward-looking skilled worker could combine the Birkett claims with the Zlotnick teachings to arrive at the presently claimed subject matter.

It is submitted that the claims here are more than a mere obvious variant of those of the Birkett patent, particularly in view of the non-relevance of the Zlotnick teachings. It is thus believed that a non-statutory double patenting rejection of these claims would be improper and should be withdrawn.

CLAIMS APPENDIX

1. (rejected) A recombinant chimer hepatitis B core (HBc) protein molecule up to about 515 amino acid residues in length that

(a) contains an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop,

(b) contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contains a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus,

said chimer molecules (i) containing no more than about 5 percent substituted amino acid residues in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149, (ii) self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and said particles are more stable than are particles formed from otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified

particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days.

2. (rejected) The recombinant HBc chimer protein molecule according to claim 1 wherein said peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope is a heterologous epitope.

3. (rejected) The recombinant HBc chimer protein molecule according to claim 2 wherein said heterologous epitope is a B cell epitope.

4. (rejected) The recombinant HBc chimer protein molecule according to claim 3 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc.

5. (rejected) The recombinant HBc chimer protein molecule according to claim 3 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present.

6. (rejected) The recombinant HBc chimer protein molecule according to claim 5 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

7. (rejected) The recombinant HBc chimer protein molecule according to claim 2 further including a peptide-bonded heterologous T cell epitope.

8. (rejected) The recombinant HBc chimer protein molecule according to claim 7 wherein said T cell epitope is peptide-bonded to the C-terminal HBc amino acid residue.

9. (rejected) The recombinant HBc chimer protein molecule according to claim 8 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBc chimer protein molecule.

10-11. (cancelled)

12. (rejected) The recombinant HBc chimer protein molecule according to claim 1 wherein said chimer contains a heterologous linker residue for a conjugated epitope.

13. (rejected) The recombinant HBc chimer protein molecule according to claim 12 wherein said heterologous linker residue for a conjugated epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 4 residues of the HBc sequence of positions 76 through 85 are present.

14. (rejected) The recombinant HBc chimer protein molecule according to claim 13 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous linker residue for a conjugated epitope.

15. (rejected) The recombinant HBc chimer protein molecule according to claim 14 that contains the HBc amino acid residue sequence of position 1 through at least position 140, plus a single cysteine residue at the C-terminus.

16. (rejected) The recombinant HBc chimer protein molecule according to claim 15 wherein said chimer contains the HBc amino acid residue sequence of position 1 through position 149.

17. (rejected) The recombinant HBc chimer protein molecule according to claim 16 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

18. (rejected) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 135 to about 515 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to one to about 245 amino

acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) one or more of residues 76 to 85 is absent;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii),

said chimer molecules self-assembling into particles on expression in a host cell, said particles being substantially free of binding to nucleic acids and more stable than are particles formed from otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days, and having an

amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

19. (rejected) The recombinant HBc chimer protein molecule according to claim 18 that contains two heterologous epitopes.

20. (rejected) The recombinant HBc chimer protein molecule according to claim 19 wherein said two heterologous epitopes are present in Domains I and II, II and IV or I and IV.

21. (rejected) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope.

22. (rejected) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a T cell epitope.

23. (rejected) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope and the other is a T cell epitope.

24. (rejected) The recombinant HBc chimer protein molecule according to claim 18 wherein said Domain I includes a heterologous epitope peptide-bonded to one of HBc residues 1-4.

25. (rejected) The recombinant HBc chimer protein molecule according to claim 24 wherein said heterologous epitope of Domain II is a B cell epitope.

26. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

27. (rejected) The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous epitope.

28. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope comprises up to about 245 amino acid residues.

29. (rejected) The recombinant HBc chimer protein molecule according to claim 28 wherein said heterologous epitope is a B cell epitope.

30. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope contains 6 to about 50 amino acid residues.

31. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope contains 20 to about 30 amino acid residues.

32. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein said Domain IV comprises 1 to about 5 cysteine residues within about 30 residues from the C-terminus of the chimer molecule.

33. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope.

34. (cancelled)

35. (rejected) The recombinant HBc chimer protein molecule according to claim 18 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

36. (rejected) The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous linker residue for a conjugated epitope.

37. (rejected) The recombinant HBc chimer protein molecule according to claim 36 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

38. (rejected) The recombinant HBc chimer protein molecule according to claim 37 that contains a single cysteine residue at the C-terminus of the HBc chimer protein molecule.

39-41. (cancelled)

42. (rejected) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 175 to about 240 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBc and constitute a heterologous epitope;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) a cysteine residue [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus,

said chimer molecules self-assembling into particles on expression in a host cell that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.2 to about 1.6 and are more stable than are particles formed from otherwise identical HBc

chimer molecules that lack said C-terminal cysteine residue or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days, and having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

43. (rejected) The recombinant HBc chimer protein molecule according to claim 42 wherein said heterologous epitope of Domain II is a B cell epitope.

44. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 15 to about 50 amino acid residues.

45. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 20 to about 30 amino acid residues.

46. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope.

47. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said B cell epitope is an amino acid sequence present in a pathogen selected from the group consisting of *Streptococcus pneumonia, Cryptosporidium parvum,* HIV, foot-and-mouth disease virus, influenza virus, *Yersinia pestis, Haemophilus influenzae, Moraxella catarrhalis, Porphyromonas gingivalis, Trypanosoma cruzi, Plasmodium falciparum, Plasmodium vivax, Plasmodium berghi, Plasmodium yoelli, Streptococcus sobrinus, Shigella flexneri,* RSV, *Plasmodium Entamoeba histolytica, Schistosoma japonicum, Schistosoma mansoni,* and ebola virus.

48. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

49. (rejected) The recombinant HBc chimer protein molecule according to claim 48 wherein said T cell epitope is from the organism against which a contemplated chimer is to be used as an immunogen.

50. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said C-terminal cysteine residue is located within about five amino acid residues of the C-terminus of the chimer protein molecule.

51. (rejected) Immunogenic particles comprising recombinant hepatitis B core (HBc) chimeric protein molecules,

said chimeric protein molecules being up to about 515 amino acid residues in length, said chimeric protein molecules

(a) containing an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule,

(b) (i) displaying one or more heterologous immunogenic epitopes at the N-terminus, HBc immunogenic loop or C-terminus, or (ii) having a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop,

(c) containing a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus, and containing a cysteine residue at or near the C-terminus,

(d) containing no more than about 5 percent substituted amino acid residues in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149,

said particle being substantially free of nucleic acid binding and exhibiting enhanced stability relative to particles comprised of otherwise identical proteins that are free of said cysteine residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days.

52. (rejected) The immunogenic particles according to claim 51 that exhibits a 280/260 absorbance ratio of about 1.2 to about 1.7.

53. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the N-terminus.

54. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the C-terminus.

55. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope in the immunogenic loop.

56. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays a B cell immunogenic epitope.

57. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays a T cell immunogenic epitope.

58. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays separate B cell and T cell immunogenic epitopes.

59. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein has a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop.

60. (rejected) The immunogenic particles according to claim 59 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

61. (rejected) The immunogenic particles according to claim 60 wherein said heterologous linker residue for a conjugated epitope is conjugated to a hapten.

62. (rejected) The immunogenic particles according to claim 61 wherein said hapten is an oligosaccharide.

63. (rejected) Immunogenic particles comprising a plurality of recombinant chimeric hepatitis B core (HBc) protein molecules;

said recombinant chimeric HBc protein molecules having a length of up to about 515 amino acid residues that

(a) contain a HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop, or a sequence of at least about 135 residues of the N-terminal 150 HBc amino acid residues,

(b) contain one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contain a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus,

said chimer molecules containing no more than 10 percent conservatively substituted amino acid residues in the HBc sequence, and

said particles being substantially free of binding to nucleic acids, and being more stable than are particles formed from ~~an~~ otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days, and having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

64. (rejected) The immunogenic particles according to claim 63 that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6.

65. (rejected) The immunogenic particles according to claim 63 wherein the length of said recombinant chimeric HBc protein molecules is about 175 to about 240 amino acid residues.

66. (rejected) The immunogenic particles according to claim 63 wherein said peptide-bonded heterologous epitope or

a heterologous linker residue for a conjugated epitope is a heterologous epitope.

67. (rejected) The immunogenic particles according to claim 66 wherein said heterologous epitope is a B cell epitope.

68. (rejected) The immunogenic particles according to claim 63 wherein the length of said recombinant chimeric HBc protein molecules is up to about 435 amino acid residues.

69. (rejected) The immunogenic particles according to claim 63 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc.

70. (rejected) The immunogenic particles according to claim 67 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present.

71. (rejected) The immunogenic particles according to claim 70 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

72. (rejected) The immunogenic particles according to claim 68 further including a peptide-bonded heterologous T cell epitope.

73. (rejected) The immunogenic particles according to claim 72 wherein said T cell epitope is peptide-bonded to the C-terminal HBc amino acid residue.

74. (rejected) The immunogenic particles according to claim 73 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBc chimer protein molecule.

75. (rejected) The immunogenic particles according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 135 to about 515 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all of the residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) the sequence of HBc at positions 76 to 85 is present free from heterologous residues;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii), said chimeric HBc protein having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

76. (rejected) The immunogenic particles according to claim 75 that contains a heterologous linker residue for a conjugated epitope in Domain II and further includes a hapten linked to said heterologous linker residue.

77. (rejected) The immunogenic particles according to claim 76 wherein said hapten is a B cell immunogen.

78. (rejected) The immunogenic particles according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 175 to about 240 amino acid residues and contain four peptide-linked amino acid residue

sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBc and constitute a heterologous epitope;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

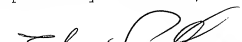
(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to about five cysteine residues [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus,

said particles exhibiting a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6, and said chimeric HBc protein having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

79-115. (cancelled)

Favorable consideration of this Appeal and allowance on the captioned application are respectfully requested.

Respectfully submitted,

By 
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Enclosures
Brief on Appeal Fee
Request for Oral Hearing and Fee

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